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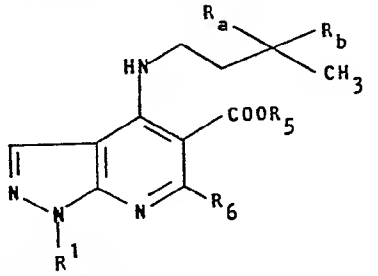
(54) **Pyrazolo(3,4-b)pyridine derivatives.**

(57) Pyrazolo[3,4-b]pyridine compounds which are useful for their activity in the central nervous system of warm-blooded animals, of the formula:



1

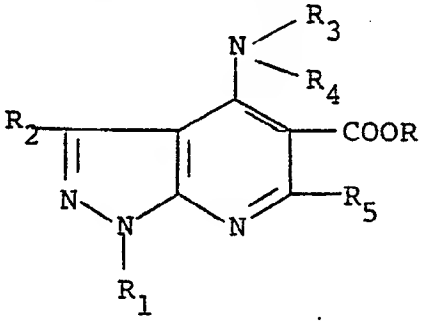
wherein R_1 is lower alkyl, R_a is hydrogen and R_b is hydroxy or R_a and R_b combine to form a = 0 group, R_5 is hydrogen or lower alkyl, and R_6 is lower alkyl, and the pharmaceutically-ecceptable salts thereof. Process for the manufacture of said compounds. Pharmeceutical compositions comprising one of said compounds and a pharmaceutically-acceptable diluent or carrier.

EP 0 076 035 A1

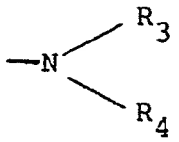
TITLE: PYRAZOLO[3,4-b]PYRIDINE DERIVATIVES

This invention relates to pyrazolo[3,4-b]-pyridine derivatives which are central nervous system depressants and may be used as tranquilizers or ataractic agents for the relief of anxiety and tension states.

In United States patent specification No. 3,755,340 there are described and claimed compounds of the following formula:



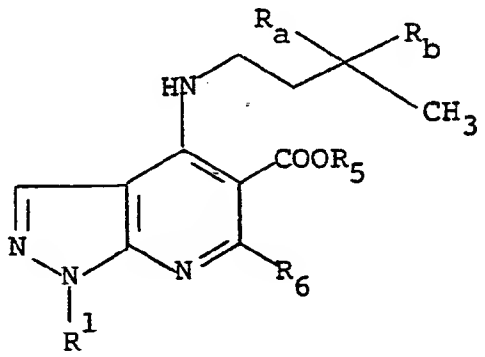
wherein R is hydrogen or alkyl of up to 12 carbon atoms, R_1 is hydrogen, lower alkyl, phenyl, benzyl, phenylethyl, benzoyl or halobenzoyl, R_2 is hydrogen, phenyl or C_1-C_3 alkyl, R_3 and R_4 each is hydrogen, lower alkyl, allyl, lower alkanoyl, R_6,R_7-phenyl, R_6,R_7-phenyl-lower alkyl, di-lower alkylamino-lower alkyl, R_6,R_7-benzoyl, methanesulphonyl, benzenesulphonyl or toluenesulphonyl, or



is pyrrolidino, R_5 is hydrogen, phenyl or C_1-C_3 alkyl,

R_6 is hydrogen, halogen, lower alkyl, trifluoromethyl, amino or carboxy, R_7 is hydrogen, halogen or lower alkyl, and physiologically-acceptable acid-addition salts thereof. The compounds are useful as ataractic, analgesic and anti-inflammatory agents. One of the compounds disclosed is 4-n-butylamino-1-ethyl-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester, which has the generic name tracazolate (see Example 67).

The present invention provides pyrazolo-pyridine compounds of the following formula (I):



I

wherein R_1 is lower alkyl; R_a is hydrogen and R_b is hydroxy or R_a and R_b combine to form a = 0, or oxo, group; R_5 is hydrogen or lower alkyl; and R_6 is lower alkyl, and pharmaceutically-acceptable salts thereof.

R_1 may more particularly be branched or straight chain lower alkyl, e.g. of 1 to 4 carbon atoms. A specific alkyl group for R_1 is ethyl.

R_5 may more particularly be branched or straight chain lower alkyl, e.g. of 1 to 4 carbon atoms. A specific alkyl group for R_5 is ethyl.

R_6 may more particularly be branched or straight chain lower alkyl, e.g. of 1 to 4 carbon atoms. A specific alkyl group for R_6 is methyl.

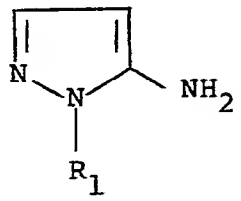
Specific compounds of the invention include those wherein R_1 is ethyl; R_a is hydrogen; R_b is hydroxy; R_5 is ethyl; and R_6 is methyl, or wherein R_1 is ethyl; R_a and R_b combine to form a = O group; R_5 is ethyl; and R_6 is methyl.

It is to be understood that various compounds within the scope of formula I exist in the form of optical isomers as is known in the art, and the present invention includes all such isomers. For example, when R_a is hydrogen and R_b is hydroxy, the carbon atom to which they are attached would be considered asymmetric, and the present invention includes both isomers which could be formed based on this asymmetry.

The pharmaceutically-acceptable salts of the invention include acid-addition salts when R_5 is lower alkyl and base-addition salts when R_5 is a hydrogen atom. Examples of suitable salts include non-toxic, physiologically-acceptable acid-addition salts such as mineral acid salts, e.g. hydrohalides, especially hydrochlorides and hydrobromides, sulfates, nitrates and phosphates. Examples of base-addition salts include alkali or alkaline earth metal salts such as sodium and potassium salts.

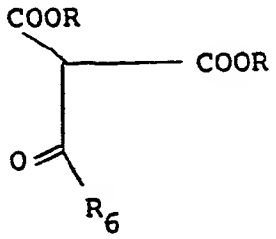
The compounds of the invention may be prepared by routes analogous to those described in

U.S. Patent 3,755,340 and more specifically as follows. An aminopyrazole of the following formula (II):



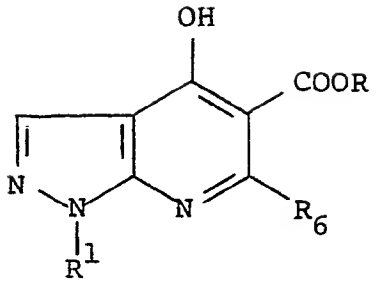
II

is prepared by ring closure of an aldehyde hydrazone of the formula $N{\equiv}CCH_2CH_2NHN{=}CHR_{10}$, wherein R_{10} is hydrogen or lower alkyl, as described in U.S. Patent 3,755,340. The compound of the formula II is then reacted, e.g. at a temperature of about 110° to 130°C in the presence of polyphosphoric acid, with an alkylcarbonyl malonic acid diester of the following formula (III):



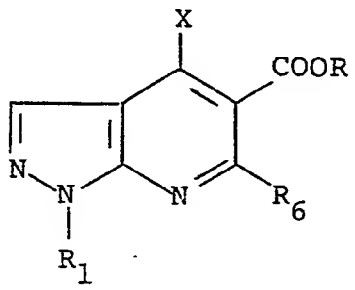
III

Compounds of the formula III are known, e.g. acetomalonic acid diethyl ester, and may be prepared by the reaction of an alkane acid chloride, e.g. acetyl chloride, with the anion of a dialkyl ester of malonic acid. The product of the reaction of a compound of the formula II and a compound of the formula III is an intermediate of the following formula (IV):



IV

wherein R is alkyl such as lower alkyl, e.g. ethyl, and R_1 and R_6 are lower alkyl. To yield the desired R_5 grouping in formula I, the -COOR moiety in IV may either be transesterified as is known in the art with a lower alkyl alcohol or saponified to yield a compound of formula I with R_5=H by reaction with an alkali metal hydroxide such as sodium or potassium hydroxide. These reactions may be carried out at this stage or after replacement of the butylamino group, although saponification, if R_5=H is desired, should preferably be carried out after placement of the butylamino. Compounds of formula IV may then be converted into a halo compound of the following formula (V):



V

wherein X is chloro or bromo, by reaction of IV with a chlorinating or brominating agent such as phosphorus oxychloride. For compounds of formula I wherein R_a and R_b combine to form =O, the corresponding compound of the formula V, X = chloro or bromo, may then be reacted with 3-oxo-n-butyl-

amine of the formula $H_2NCH_2CH_2COCH_3$. The keto group of the 3-oxo-n-butylamine may have to be protected prior to the reaction, e.g. by use of a corresponding ketal. For compounds of formula I wherein R_a is hydrogen and R_b is hydroxy, the corresponding compound of the formula V, X=chloro or bromo, is reacted with 3-hydroxy-n-butylamine of the formula $H_2NCH_2CH_2CHOHCH_3$. Alternatively, the corresponding compound of formula V, X=chloro or bromo, is first reacted with ammonia to give a compound of formula V, $X=NH_2$, which is then reacted with 1-halo-3-hydroxy-n-butane, e.g. 1-bromo- or 1-chloro-3-hydroxy-n-butane.

Starting materials of formula III may be prepared by methods generally described in Organic Syntheses, Coll. Vol. IV, pages 285-288 (1963).

3-oxo-n-butylamine and its ketal may be prepared by the process of reacting phthalimide with methyl vinyl ketone to give N-(3-oxo-n-butyl)-phthalimide which is then reacted with ethylene glycol to yield the corresponding ketal. The ketal is then reacted with hydrazine to remove the phthalic acid moiety and yield the ketal of 3-oxo-n-butylamine. Reaction of the ketal with dilute hydrochloric acid yields the HCl salt of 3-oxo-n-butylamine and the free amine can be obtained by basification with sodium bicarbonate.

3-hydroxy-n-butylamine may be prepared by first reacting 1-chloro-2-propanol with potassium cyanide to yield 3-hydroxybutyronitrile which is

then hydrogenated with Raney nickel to give 3-hydroxy-n-butylamine.

The pharmaceutical compositions of the invention may be prepared and used according to methods known for the compounds cartazolate and tracazolate. Specifically, the new compounds of this invention are central nervous system depressants and may be used as tranquilizers or ataractic agents for the relief of anxiety and tension states, for example in mice, cats, rats, dogs and other mammalian species, in the same manner as chlordiazepoxide. For this purpose a compound or mixture of compounds of formula I, or non-toxic physiologically-acceptable acid-, if R_5 = alkyl, or base-, if R_5=H, addition salt thereof, may be administered orally or parenterally in a conventional dosage form such as a tablet, pill, capsule, injectable or the like. A single dose, or preferably 2 to 4 divided daily doses, provided on a basis of about 1 to 50mg per kilogram of body weight per day, preferably about 2 to 15mg per kilogram per day, is appropriate. These may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250mg per unit dosage with conventional vehicle, excipient, binder, preservative, stabilizer, flavour or the like as called for by accepted pharmaceutical practice, e.g. as described in U.S. Patent 3,755,340.

Compounds of the invention have been shown to suppress CNS activity in warm blooded animals and particularly to suppress anxiety. Among the tests conducted to demonstrate the anxiolytic activity

of the present compounds was the Shock-Induced Suppression of Drinking (Rats) (SSD) Test, which was carried out as follows:

Male rats in the weight range of 200 to 220 grams are water-deprived for 48 hours and food-deprived for 24 hours before testing. Normally, the rats are orally intubated (5ml/kg) with the test compound (based on mg/kg body weight). The vehicle control group of rats is also intubated by mouth. A positive control group of rats is also orally administered a control dose of 18mg/kg of chlordiazepoxide. Radomization is utilized in dosing. The rats are returned to the cage for one hour. Sixty minutes after drug administration, the rat is quietly removed from its cage and the hind feet wiped with Signa electrode gel made by Parker Laboratories of Orange, N.J. When intra-peritoneal (i.p.) administration was used, the protocol was identical except that the drugs were administered (5ml/kg) 30 minutes prior to testing. The rat is placed on the floor in the chamber facing the licking tube. The animal is allowed 5 minutes to make 20 licking responses and receive the first shock (0.5 mA). If this does not occur, the animal is removed and eliminated from the study. If 20 licking responses are made, the animal is permitted an additional 3 minutes during which time each 20th lick is paired with a 0.5 mA shock. This period is automatically started, counted and terminated. The number of licks and shocks are recorded. The activity of the compound tested is evaluated by

comparing the mean shocks of the group dosed with the test compound to both the mean shocks of the vehicle and positive control groups via a Students' t-test. The higher the number of shocks received the higher the anti-conflict or anti-anxiety activity of the compound.

In the SSD test, the compound of the invention of formula I wherein R_1 is ethyl; R_a is hydrogen; R_b is hydroxy; R_5 is ethyl; and R_6 is methyl showed activity at 20mg/kg i.p. indicated by a significant (less than 0.05, Students' t-test) increase in the number of shocks taken. Further, the compound of the invention of formula I wherein R_1 is ethyl; R_a and R_b combine to form a = O group; R_5 is ethyl; and R_6 is methyl showed activity at 40mg/kg per os as determined by a significant (less than 0.05, Students' t-test) increase in the number of shocks taken. No toxic effect was observed with either compound at the stated dose.

Synthesis of compounds of the invention is demonstrated by the following Examples, degrees being in Centigrade (C) and the following abbreviations being used: mg (milligrams), kg (kilograms), g (grams), psi (pounds per square inch pressure), mMole (millimole), ml (millilitres) and mp (melting point). Conventional chemical abbreviations for the elements, e.g. C, H, N and O, are also used.

Example 1

(a) 1-Ethyl-6-methyl-4-hydroxy-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid ethyl ester

51.1g of 1-ethyl-5-aminopyrazole (0.46 mole) and 101g of acetomalonic acid ethyl ester (0.5 mole) were added to 224g of polyphosphoric acid. The mixture was heated with stirring at 120° for three hours. After this period, the mixture was cooled, diluted with 1,000ml of water and subsequently extracted twice with 300ml portions of chloroform. The chloroform layers were collected, dried over sodium sulfate, and the solvent was distilled off. Recrystallization of the residue (67g) with petroleum ether yielded 1-ethyl-6-methyl-4-hydroxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester, mp 118-120°C.

(b) 4-Chloro-1-ethyl-6-methyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid ethyl ester

A mixture of 49.1g of 1-ethyl-6-methyl-4-hydroxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.197mole) and 250ml. of phosphorus oxychloride was refluxed for 4 hours. Then the excess phosphorus oxychloride was removed by vacuum distillation and the residue was treated with water. The 4-chloro compound (42g) was filtered under suction and recrystallized from n-hexane, mp 54-56°C.

(c) 3-Hydroxybutyronitrile

A mixture of 109.15g of 1-chloro-2-hydroxy-propane (1.15 mole), 109.2g of KCN (1.68 mole), and

16.4g (0.086 mole) of KI in 600 ml of a mixture of 5:1 by volume ethanol:water was heated under reflux for 10 hours, then cooled to room temperature and filtered. The filtrate was concentrated in vacuo and extracted with 4 washings of 200ml of diethyl ether each. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to yield 62.7g of crude product. The product was flash distilled to yield 45.1g of product.

(d) 3-Hydroxy-n-butylamine

A mixture of 25.04g of 3-hydroxybutyronitrile (0.294 mole) in 300ml of ammonia-saturated methanol was hydrogenated at 50 psi over 25g of Raney Nickel with H_2 at room temperature for 7 hours. Catalyst was removed by filtration and the filtrate was concentrated in vacuo to yield 26.3g of crude product which was partially purified by flash distillation to give 20.84g (80% yield) of product.

(e) 1-Ethyl-4-(3-hydroxy-n-butylamino)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

2.75 each of 4-chloro-1-ethyl-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester and 3-hydroxy-n-butylamine were combined with 15.6ml of dry toluene under N_2 and heated at 45°C for 48 hours. The mixture was cooled to room temperature and the toluene layer was decanted from the

oil that separated out. The toluene layer was washed with water and then dried and concentrated in vacuo to yield 3.7g of product which crystallized on trituration with hexane. This was recrystallized from hexane to yield 1.91g of white product, mp 94.5-96.5°C.

Example 2

(a) 3-Oxo-n-butylamine ketal

1. A mixture of 18g (0.122 mole) of phthalimide, 8.7g (0.12 mole) of methyl vinyl ketone and 70 ml of ethyl acetate was prepared. To this was added 3ml of trimethyl benzyl ammonium hydroxide catalyst and the mixture was heated under reflux for 1/2 hour. The mixture was concentrated in vacuo to yield 37g of tan solid product. The product was recrystallized from ethanol to yield 23.01g of product, mp 107-111°C.

2. A mixture of 22.9g (0.105 mole) N-(3-oxo-n-butyl)phthalimide, 9.95g (0.160 mole) of ethylene glycol, and 0.3g of para-toluenesulphonic acid in 450ml of dry toluene under nitrogen atmosphere was heated under reflux for three hours while water was continuously removed. The mixture was cooled to room temperature and washed successively with an aqueous 5% Na_2CO_3 solution and water. The organic phase was dried and concentrated to yield 26.9g of product, mp 118-122°C.

3. A mixture of 15g (57.4 mMole) of N-(3-oxo-n-butyl)-phthalimide ketal and 3g (60 mMole) of hydrazine hydrate in 250ml H_2O was heated under reflux for 1 hour, then stirred overnight at room

temperature. The mixture was treated with 2.4g (60.3 mMole) of NaOH in 75ml of water and continuously extracted with 750ml of diethyl ether for 72 hours. The ether was tested for peroxide formation, and then dried and concentrated in vacuo. The product was flash distilled to yield 3-oxo-n-butylamine ketal.

(b) 1-Ethyl-6-methyl-4-(3-oxo-n-butylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester ketal

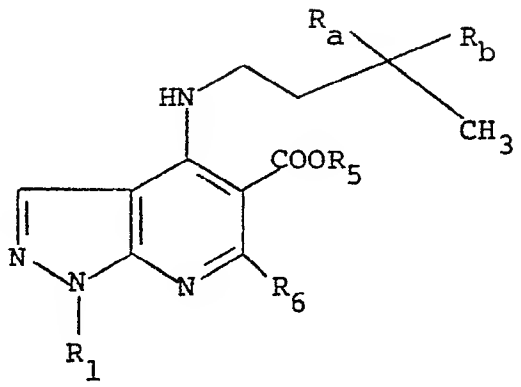
A mixture of 0.25g (0.93 mMole) of 1-ethyl-6-methyl-4-chloro-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester, 0.13g (0.99 mMole) of 3-oxo-n-butylamine ketal and 0.12g (1.2 mMole) of triethylamine in 1.5 ml of toluene was heated at 60°C for 4 hours, after which an additional equivalent (0.93 mMole) of triethylamine was added. The mixture was further heated at 60°C for an additional 12 hours. The top layer was decanted off, washed with a 2% $NaHCO_3$ aqueous solution, dried and concentrated to yield 0.38g of product which crystallized on standing. The product was recrystallized from hexane to yield 0.26g of 1-ethyl-6-methyl-4-(3-oxo-n-butylamino)-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid ethyl ester ketal, mp 69-72°C.

(c) 1-Ethyl-6-methyl-4-(3-oxo-n-butylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

A mixture of 3.65g of 1-ethyl-6-methyl-4-(3-oxo-n-butylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester ketal in 45ml of tetrahydrofuran and 22 ml of a 10% HCl aqueous solution was stirred overnight at room temperature. The mixture was basified with a 20% $NaHCO_3$ aqueous solution and extracted with ether. The ethereal phase was dried and then concentrated to yield 3.2g of a white solid product which was recrystallized from hexane to yield 3.09g of the ethyl ester of 1-ethyl-6-methyl-4-(3-oxo-n-butylamino)-1H-pyrazolo-[3,4-b]pyridine-5-carboxylic acid, mp 84.5-86.5°C.

What is claimed is:-

1. A pyrazolopyridine compound of the following formula (I)



I

wherein R_1 is lower alkyl; R_a is hydrogen and R_b is hydroxy or R_a and R_b combine to form a = O group; R_5 is hydrogen or lower alkyl; and R_6 is lower alkyl, or a pharmaceutically-acceptable salt thereof.

2. A pyrazolopyridine as claimed in Claim 1, wherein R_1 is ethyl.

3. A pyrazolopyridine as claimed in Claim 1 or 2, wherein R_a is hydrogen and R_b is hydroxy.

4. A pyrazolopyridine as claimed in Claim 1 or 2, wherein R_a and R_b combine to form a = O group.

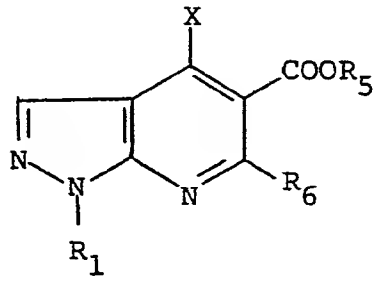
5. A pyrazolopyridine as claimed in any one of Claims 1 to 4, wherein R_5 is ethyl.

6. A pyrazolopyridine as claimed in any one of Claims 1 to 5, wherein R_6 is methyl.

7. The pyrazolopyridine claimed in Claim 1, wherein R_1 and ethyl;
R_a is hydrogen and R_b is hydroxy;
R_5 is ethyl; and
R_6 is methyl.

8. The pyrazolopyridine claimed in Claim 1, wherein R_1 is ethyl;
R_a and R_b combine to form a = 0 group;
R_5 is ethyl; and
R_6 is methyl.

9. A process for the manufacture of a compound of formula (I), wherein R_1, R_a, R_b, R_5 and R_6 have the meanings stated in Claim 1, or a pharmaceutically-acceptable salt thereof, which comprises reacting a compound of formula (Va)



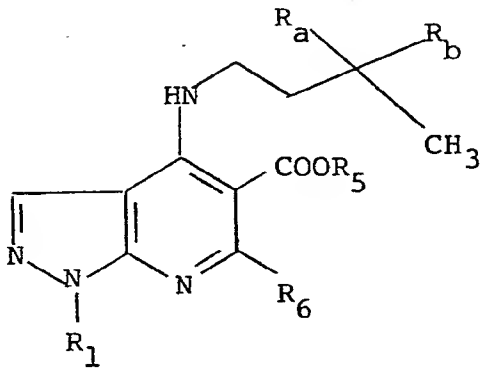
Va

wherein R_1, R_5 and R_6 have the meanings stated in Claim 1 and X is chloro or bromo, with 3-oxo-n-butylamine, a ketal of 3-oxo-n-butylamine, or 3-hydroxy-n-butylamine.

10. A pharmaceutical composition comprising a pyrazolopyridine as claimed in Claim 1, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

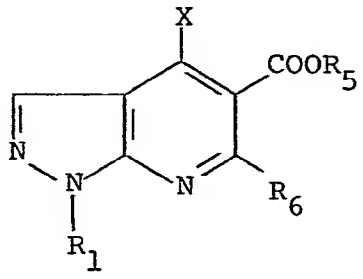
ICI Americas Case 1550-1 Claims for Austria

1. A process for the manufacture of a pyrazolo-pyridine compound of the following formula (I)



I

wherein R_1 is lower alkyl; R_a is hydrogen and R_b is hydroxy or R_a and R_b combine to form a = 0 group; R_5 is hydrogen or lower alkyl; and R_6 is lower alkyl, or a pharmaceutically-acceptable salt thereof, which comprises reacting a compound of formula (Va)



Va

wherein R_1, R_5 and R_6 have the meanings stated above and X is chloro or bromo, with 3-oxo-n-butylamine, a ketal of 3-oxo-n-butylamine, or 3-hydroxy-n-butyl-amine.

2. A process as claimed in Claim 1 wherein R_1 is ethyl; R_a is hydrogen; R_b is hydroxy; R_5 is ethyl; and R_6 is methyl.

3. A process as claimed in Claim 1 wherein R_1 is ethyl; R_a and R_b combine to form a = 0 group; R_5 is ethyl; and R_6 is methyl.

R. Allerton

ROY ALLERTON

AUTHORISED REPRESENTATIVE
General Authorisation No. 97

RA/LMS : ICI Americas Case 1550-1/OEE
22 Jul 82

European Patent Office

EUROPEAN SEARCH REPORT

0076035
Application number

EP 82 30 4483

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
D,A	US-A-3 755 340 (H.HOEHN) *Claim 1; column 7, lines 28-67; column 8, line 1-7*	1,10	C 07 D 471/04 A 61 K 31/44 // (C 07 D 471/04 C 07 D 231/00 C 07 D 221/00)

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 471/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	21-12-1982	ALFARO I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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